Lifetime Risk of Melanoma in CDKN2A Mutation Carriers in a Population-Based Sample

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Background: Germline mutations in the CDKN2A gene have been linked to melanoma incidence in many families with multiple cases of the disease. Previous studies of multiple-case families have indicated that the lifetime risk (i.e., penetrance) of melanoma in CDKN2A mutation carriers is very high, ranging from 58% in Europe to 91% in Australia by age 80 years. In this study, we examined lifetime melanoma risk among CDKN2A mutation carriers using carriers who were identified in a population-based study of melanoma.

Methods: Probands for the study were incident case patients with either first or subsequent melanoma who were identified in nine geographic regions in Australia, Canada, the United States, and Italy. A total of 3626 probands (53% participation rate) with adequate DNA for analysis were recruited and genotyped for CDKN2A mutations. From the 3550 probands whose DNA could be amplified by polymerase chain reaction of CDKN2A exons 1 α , 2, and 3 and surrounding regions, 65 mutation carriers were identified. Melanoma histories in first-degree relatives of these probands were used to calculate the lifetime risk in CDKN2A mutation carriers using the kin – cohort method.

Results: The risk of melanoma in CDKN2A mutation carriers was approximately 14% (95% CI = 8% to 22%) by age 50 years, 24% (95% CI = 15% to 34%) by age 70 years, and 28% (95% CI = 18% to 40%) by age 80 years. Eighteen probands had three or more first-degree relatives with melanoma, but only one was a carrier of a CDKN2A mutation.

Conclusions: CDKN2A mutation carriers in the general population have a much lower risk of melanoma than that suggested by estimates obtained from multiple-case families. The preponderance of familial clustering of melanoma occurs in families without identifiable mutations in CDKN2A.

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